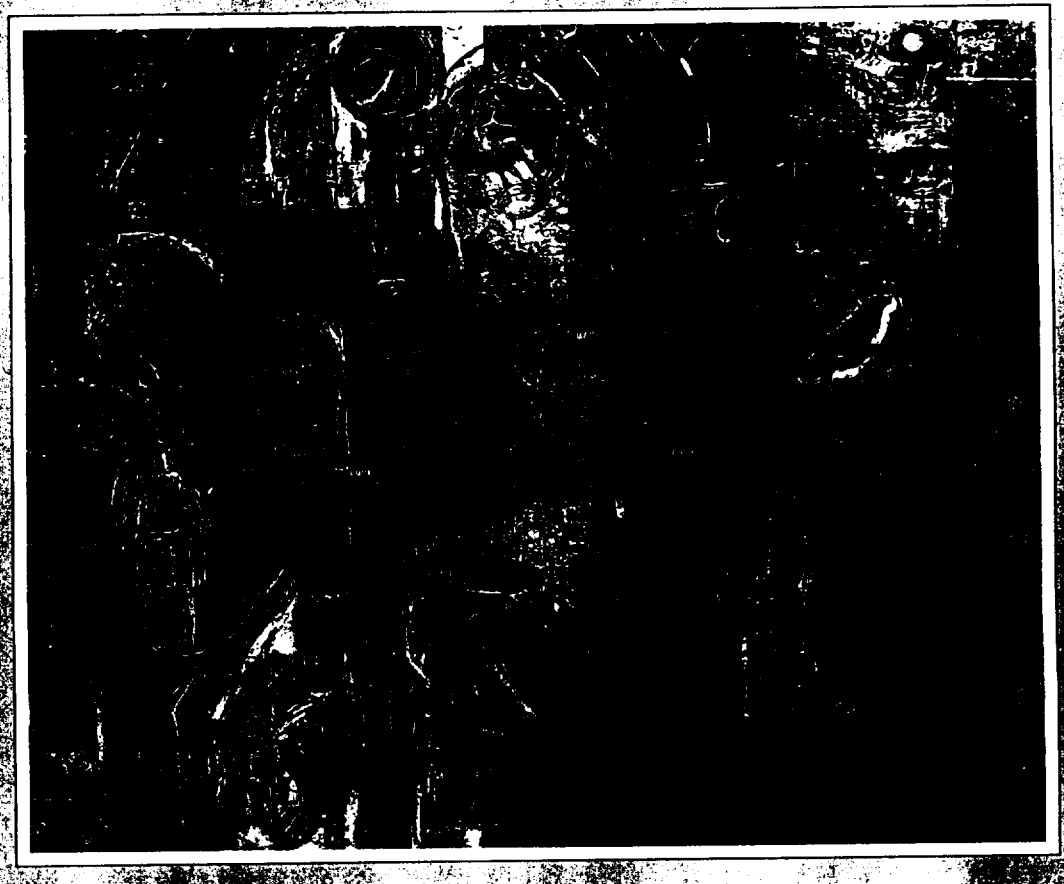
ABCC/RERF: Commemorating the First 50 Years and Looking to the Future

ABCC/放影研：50周年を記念し将来を展望する



National Academy of Sciences Auditorium
Washington, D.C. June 13–14, 1997

米国学士院 講堂
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In 1946, President Harry Truman, in a document currently on display at the entrance to this auditorium, approved a directive to the National Academy of Sciences–National Research Council (NAS–NRC) to initiate a long-term investigation of the health effects associated with exposure to radiation from the atomic bombs. With funding provided by the Atomic Energy Commission, now the Department of Energy, NAS–NRC established the Atomic Bomb Casualty Commission (ABCC) in March 1947. The government of Japan, through the Japanese National Institute of Health, became a partner in that endeavor in 1948. In 1975, the Radiation Effects Research Foundation (RERF) was established and assumed the responsibilities of ABCC.

This symposium commemorates 50 years of ABCC/RERF. It is dedicated to the many survivors and their families without whose cooperation we would not have learned as much as we have about the effects of radiation. It is also dedicated to the thousands of employees of RERF and scientists around the world who have contributed through the years to the analysis and interpretation of the information emerging from this unique study.

In the spirit of commitment to the importance of continuing the pursuit of further information, and with half of the original survivors who remain alive today entering their cancer-prone years, the scientific component of the symposium is looking to the future. RERF scientists will present the results of their latest work and will discuss their future directions and goals. Panels composed of distinguished scientists will contribute their thoughts and bring their unique perspectives to the discussion of these goals.

ABCC/RERF: COMMEMORATING THE FIRST 50 YEARS AND LOOKING TO THE FUTURE
National Academy of Sciences Auditorium
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June 13, 1997

09:00–09:45 Commemorative Ceremony
- Greetings from Dr. Bruce Alberts, *President National Academy of Sciences*
- Greetings from Dr. Itsuzo Shigematsu, *Chairman Radiation Effects Research Foundation*
- Greetings from Dr. Tara O'Toole, *Assistant Secretary US Department of Energy*
- Greetings from Mr. Shotaro Oshima, *Minister Embassy of Japan (US)*

09:45–10:00 Break

10:00–10:05 Introduction of panel moderators by Dr. Charles Land *US National Institutes of Health, National Cancer Institute*

10:05–10:55 Panel on ABCC:
- Dr. Gilbert Beebe, *Moderator*
- Dr. Hiroshi Maki
- Mr. Michael Rappaport
- Dr. Robert Miller
- Dr. James Neel

10:55–11:45 Panel on RERF:
- Dr. Stuart Finch, *Moderator*
- Dr. Tsutomu Sugahara
- Mr. Seymour Jablon
- Dr. William Schull
- Dr. Charles Edington

11:45–11:50 Words of appreciation from Dr. Evan Douple, *Director Board on Radiation Effects Research*

11:50–13:00 Lunch in the Great Hall of the Academy building

June 13, 1997

13:00–17:30 Scientific Session I (Auditorium)

Moderators: Itsuzo Shigematsu and Paul Gilman
Chairman, RERF — *Executive Director, Commission on Life Sciences, NAS*

Topic	Panel Co-Chairs	Invited Panelists
1. RISK ESTIMATION	*Dale Preston *Dept. of Statistics, RERF*	*Albrecht Kellerer *University of Munich*
	*Kiyohiko Mabuchi *Dept. of Epidemiology, RERF*	Geoffrey Howe *Columbia University*
		Susan Preston-Martin *University of Southern California*
		Ethel Gilbert *US National Cancer Institute*
2. NONCANCER END POINTS	*Kazunori Kodama *Dept. of Clinical Studies, RERF*	*Steven Lipshultz *Rochester University*
	*Masazumi Akahoshi *Dept. of Clinical Studies, RERF*	Eric Boerwinkle *University of Texas Health Science Center at Houston*
		Baruch Blumberg *Fox Chase Cancer Center*
3. MOLECULAR AND GENETIC BASIS OF CANCER	*Toshio Seyama *Dept. of Radiobiology, RERF*	*Curtis Harris *US National Cancer Institute*
	Kiyohiko Mabuchi *Dept. of Epidemiology, RERF*	Maurice Fox *Massachusetts Institute of Technology*
		Tyler Jacks *Massachusetts Institute of Technology*

*Denotes keynote panel presenter

June 14, 1997

08:30–12:30 Scientific Session II (Auditorium)

Moderators: Evan Douple and Sheldon Wolff

Director, Board on Radiation Effects Research, NAS

Vice-Chairman and Chief of Research, RERF

4. RERF DOSIMETRY	*Dale Preston *Dept. of Statistics, RERF*	*Tore Straume *University of Utah*
	*Nori Nakamura *Dept. of Genetics, RERF*	Warren Sinclair *National Council on Radiation Protection & Measurement*
		Masaharu Hoshi *Hiroshima University*
		John Zimbrick *Purdue University*
5. STUDIES OF THE F_1 POPULATION	*Chiyoko Satoh *Dept. of Genetics, RERF*	*James Neel *University of Michigan*
	*Kiyohiko Mabuchi *Dept. of Epidemiology, RERF*	Seymour Abrahamson *University of Wisconsin*
		William J. Schull *University of Texas Health Science Center at Houston*
6. TRAINING COLLABORATIONS	*Akio Awa *Assistant Chief of Research, RERF*	*Niel Wald *University of Pittsburgh*
	Joseph Weiss *US Department of Energy*	Elaine Ron *US National Cancer Institute*
		Joel Breman *US National Institutes of Health*
		Jaak Sinnaeve *European Commission*

Symposium Summation: Roger H. Clarke

Director, National Radiological Protection Board, UK

* Denotes keynote panel presenter

About the cover–

"Experimental Laboratory—Small Life" was painted by Torao Sasaki, currently the assistant chief of the secretariat at the Radiation Effects Research Foundation in Hiroshima and an RERF employee for 37 years. Mr. Sasaki's painting received a special award in 1993 at the 25th Nitten, a national art exhibit by members of a prestigious Japanese association of artists.

表紙について－

「実験室・小さき命」は、現在広島放射線影響研究所 事務局次長であり、同所勤続37年の佐々木寅夫氏により描かれたものである。佐々木氏のこの絵画は、日本の著名な総合美術展・日展（第25回 1993年）で特選を受賞した作品である。

SUBMITTED ABSTRACTS

ABCC/RERF: COMMEMORATING THE FIRST 50 YEARS AND LOOKING TO THE FUTURE

50th Anniversary Symposium
National Academy of Sciences
Washington, DC
June 13-14, 1997

Dr. Bruce Alberts, President, National Academy of Sciences

Dr. Itsuzo Shigematsu, Chairman, Radiation Effects Research Foundation

I sincerely congratulate you on this auspicious occasion of the 50th anniversary of ABCC/RERF. I am very pleased and would like to thank you cordially for offering me the opportunity to attend this celebratory event and see you here today.

I understand that in 1947, the Ministry of Health and Welfare (MHW) was approached through the General Headquarters (GHQ) to conduct collaborative medical studies on radiation effects in consequence of which the Japanese National Institute of Health (JNIH) established branch laboratories for collaborative studies with ABCC. And I was asked to participate in those collaborative studies. I was hesitant about changing my job, but my mentor Professor Harumichi Oka strongly advised me to go to ABCC, and I went to Hiroshima in the summer of 1948. I retired after three years of service at the Radiation Effects Research Foundation, which was established in April 1975.

We had to have the understanding of the people participating in the long-term studies as well as of the citizens, and the cooperation of the ABCC staff. Successive ABCC directors were mindful of these needs. They also made efforts to deepen the understanding of various government offices and agencies, medical associations, and medical institutions and to strengthen cooperation with them. I would like to note in particular that Dr. George B. Darling endeavored to improve the research institute in general, including its facilities and administrative procedures during his more than 15 years' stay in Japan.

Dr. Darling established a Japanese advisory committee with the director of JNIH as its chairman, and invited experts from universities, research institutes and medical associations in Japan to serve as its members.

Around 1971 or 72, at a meeting of the Japanese advisory committee. Dr. Darling broached the idea of reconstituting ABCC into a new bilateral foundation as a non-profit foundation under Japanese law, and this subsequently came to be discussed at the top level. Finally on April 1, 1975, the Radiation Effects Research Foundation was established and took over the activities of ABCC-JNIH.

We should not forget that the 50-year-long research studies of ABCC-JNIH/RERF were rendered possible by the active involvement of the staff and the cooperation of the study participants. Many employees have passed away during the past 50 years. May their souls rest in peace. Wishing RERF further prosperity in the future, I would like to conclude my words of greeting.

ABCC-RERF Commemorative Ceremony Panel on ABCC

M. E. Rappaport

I am very grateful to Dr. Shigematsu for making this visit possible and to Dr. Douple for inviting me to join the panel on ABCC.

I have been often introduced to ABCC-RERF newcomers and visitors as one who has been with the organization from year one. Actually, when I joined ABCC in March 1949, there were perhaps 400 employees working busily in Hiroshima, Nagasaki, Kure, and Tokyo.

I was hired as Associate Engineer in the Construction Department, headed by Homer Pfeiffer, Architect-in-Charge. Pfeiffer and Associate Engineer George Friend gave me a short briefing on the scope of construction which was to consist of a clinic and laboratory in Hiroshima, a virtually identical facility in Nagasaki, and two more laboratories in Kure and Sasebo of the same design, intended for control studies.
Each of the four designs comprised five 2-story reinforced concrete buildings sheathed in specially manufactured Quonset huts, as well as connecting corridors and reception areas.

The construction of the first of these, at Hijiyama, was to start in June 1949 and in the meantime research and supporting activities proceeded, in Hiroshima, in a former Japanese Army building in Ujina and a temporary clinic in Kure. In Nagasaki ABCC rented a building from the Nagasaki Prefectural Teachers Maintenance Association, and fitted it out as a temporary laboratory. Its name was shortened to Nagasaki Kaikan or just Kaikan.

Of the sweeping plan of four new clinics, only the Hijiyama one was constructed. The Kure and Saseho projects were abandoned when it became possible to identify control populations in the two bombed cities. The Nagasaki project, which was to be built on the site of a prison destroyed by the bomb, was canceled when it became possible to satisfy research needs in the renovated Kaikan.

To "highlight successes" in our early efforts to provide space, I would say that construction of the Hijiyama Laboratory was the major highlight. It was completed in 1950 as designed, in contracted time, and within the budget provided. It brought to Japan the latest American building materials, hospital and laboratory equipment, and won Contractor-of-The-Year award for the builder.

To this success can be contrasted our failure to foresee the space needs at Hijiyama and Nagasaki Kaikan. It took several more years to obtain funds for and construct, additional buildings needed to accommodate all operations in Hiroshima and

Nagasaki. Incidentally, by the time the Kure phase was canceled, materials for Kure had already been ordered and were on the way to, or arriving in, Japan. We had considerable difficulties in storing them and even more trouble accounting for them.

Other difficulties were numerous but never insuperable. The procurement of local materials, such as cement, piping, pipe fittings, even lumber and gravel, was time-consuming in a country which had only recently begun to recover from the turmoil of war and its aftermath. Access to adequate utilities was a constant problem, especially water, electric power and telephone lines. We managed because in both Hiroshima and Nagasaki the City Authorities were cooperative and helpful. On one occasion the Mayor of Hiroshima, Shinzo Hamai, personally intervened and ordered the Water Board to expedite reconstruction of a pumping station supplying water to Hijiyama.

We were fortunate in the early stages in recruiting a staff of engineers and architects who proved competent, energetic and dedicated to the project. Some of them chose to remain at ABCC after the major construction was finished and served effectively in various technical and supervisory positions.

Thank you.

(Translation)

The 50 years of ABCC/RERF

Tsutomu Sugawara

I served RERF as a scientific councilor and then a visiting director for a total of 18 years since establishment of RERF in 1975. However, I had already had some relation with ABCC just before it moved to Hijiyama in 1950. At that time I was about to graduate from Osaka University Faculty of Sciences, where I studied while moonlighting as a doctor, and was looking for a job. ABCC asked Kyoto University to recommend someone for employment, and Kyoto University recommended me because I had studied medicine and physics. I went to Ujina for a job interview. I was looking forward to being employed, hoping to escape from a needy life of a student who lived with a wife and child in a very small six-mat room.* However, my dream vanished mercilessly when a telegram arrived which said that I was not acceptable because of my questionable background." I assume the problem was that I worked to earn my living in a clinic affiliated with communists.

I finally got a job in the Department of Internal Medicine, Mie Prefectural Medical University, and then after working in the National Institute of Genetics and the National Institute of Radiological Sciences, I became professor at Kyoto University in 1961. When I visited RERF as a scientific councilor in 1975, 25 years after it had turned down my application, my heart was full of deep emotion. Even before that, having recommended the cytogeneticists who visited me while they worked at ABCC that they should start a chromosome examination program at ABCC, I was delighted when I heard that ABCC had started to examine chromosomes in 1965. The Radiation Biology Center of Kyoto University was established in 1976, the year following the year in which ABCC was reorganized into RERF. With the dream of developing one consolidated program for the study of radiobiology in Japan through the movement for establishing the center, I approached ABCC. According to the notes I took, we held a meeting of Japan Late Effects Group (JLEG) in December 1974 and invited Dr. Beebe to it. I was surprised to find how isolated ABCC was from other Japanese researchers.

ABCC such as it was has been reorganized into RERF, which is now generally acknowledged as an international research institute funded by the US and Japan. I feel most delighted as a person who has been involved even in a small way. In retrospect, increase of malignancies other than leukemia gradually became evident around 1970, and the studies on those malignancies became a major task of RERF as it was established, and attracted the attention of the whole world. I appreciate the efforts made by the successive chairmen and researchers who endeavored to analyze the precious data collected and present the results to the world.

If there was anything we were able to do to be of some help as persons outside the foundation, that could probably be divided into three steps. The first step was to serve as a bridge between the foundation and A-bomb survivors. Dr. Iijima in particular worked hard in this area. I was led to think once again what was important for the smooth conduct of epidemiological studies. The next step was to serve as a bridge to Japanese researchers. Nowadays RERF is not greatly different from universities in our mind, but in the beginning it

was almost a completely different world. Although RERF was in Japan, it had little relationship with universities in Japan while it maintained close contact with universities in the US. There must have been many things that Japanese universities could have learned from RERF in those days. Lately universities talk about "self reviews" and "peer reviews," but at RERF scientific councilors have had such a practice since its establishment. This practice must have been taken for granted in the US, but it was exceptional in Japan those days. I used the experience and established the peer review system in the ongoing Japan-China collaborative epidemiological study. Japanese universities have just begun practicing the peer review recently. In this respect, I believe it is important for Japanese researchers to be involved not only in the conduct of collaborative studies but also in all aspects of RERF's operation and learn from the experiences. In this sense, I welcome the recommendations recently made by the Blue Ribbon Panel.

I am proud that I was able to contribute to RERF in some measure by initiating a movement with other fellow researchers in Japan to appeal to the world the importance of continuing RERF research studies when the continuation of RERF operation became an issue.

Lastly, I would like to express the hopes for the future RERF. Last year I reviewed the studies conducted at RERF and Japanese universities from the viewpoint of low dose radiation. I had the impression that, while universities were conducting a variety of studies on carcinogenesis, RERF seemed to adhere to one hypothesis. In addition, although radiation-induced solid cancer incidence observed epidemiologically has been said to show a pattern very similar to the background solid cancer incidence, different findings are reported now. Based on these points, I would like to make the following three requests:

1) RERF epidemiological data are the basis of all studies. Therefore, instead of making a new interpretation each time a new data set is added, RERF should present and make clear what has changed and what has not changed at each step of research.

2) Much of the mechanism of carcinogenesis is still unclear. Therefore, RERF should always try to develop and expand studies including collaborative studies with other institutes from various viewpoints. I believe this point was stated in the recommendations of the Blue Ribbon Panel.

3) RERF should make meetings held at RERF open to scientists in Japan as much as possible. I mention it, hoping that Japanese scientists will become more problem-conscious and learn various methods available for evaluation, and that RERF serve as a role model.

Wishing RERF continued prosperity as it celebrates its 50-year anniversary, I would like to conclude my words of greeting. Thank you.

To ABCC/RERF 50 Years' Commemorating Ceremony

I wish you success in this Commemoration and look forward to your having a very fruitful symposium. Although I was invited to this event, I regret I am unable to attend.

When I look back, my first experience in U.S. - Japan cooperation was through joint work in October and November of 1945 with a U.S. survey team of the A-bomb survivors.

Later, in 1964 and 1972, I cooperated with a U.S. medical team to investigate the Marshallese exposed to the radioactive fallout in March, 1954. At that time, we received cooperation from the ABCC.

Presently, I am serving as a part-time Director of the RERF. In this way, I will continue to contribute to U.S. - Japan cooperation.

In celebration of this historic commemoration, let me further wish you progress in your continuing study and research.

Dr. Toshiyuki Kumatori
Chairman of Radiation Effects
Association and
Director of Radiation Effects
Research Foundation

Cancer Risk Estimation in the Atomic Bomb Survivors

Dale Preston, Radiation Effects Research Foundation
ABCC/RERF 50th Anniversary Commemorative Symposium
Washington DC
June 13-14 1997

Analyses of cancer risks in the ABCC/RERF Life Span Study (LSS) have shown that the risk of cancer increases with increasing radiation dose. These excess risks persist for 50 years and are likely to be elevated until the end of life. Indeed, for cancers other than leukemia, the rate at which excess cancers are seen appears to increase throughout the lifetime of the exposed.

The most recent published report on cancer mortality in the LSS is for the period from 1950 through 1990. The results indicate that, among the roughly 50,000 cohort members with radiation doses in excess of 5 mSv, about 335 of 4565 solid cancer deaths and about 87 of the 176 leukemia deaths are associated with radiation exposure. More than 50% of the LSS cohort members are still alive (more than 90% of those exposed as children).

In this presentation I will review our recent results and briefly note various issues of current interest with regard to the description of cancer (and non-cancer) risks in the LSS.

Summarizing radiation-related risks

There is no such thing as *the risk* of radiation in a sense that can be usefully summarized in a single number. Excess risks for solid cancers in the Life Span Study appear to be quite linear in dose; however excess relative risks exhibit significant dependence on sex and age at exposure (or attained age). Leukemia excess risks appear to be nonlinear in dose with lower doses having a smaller effect than one would predict based on a linear extrapolation from high doses. However, leukemia excess risks vary dramatically with sex, age at exposure, and time to the extent that any simple (i.e. single number) summary of *the* excess risk of leukemia provides little useful information about risk.

This situation is further complicated by the fact that what one says about factors that affect the risk depends on the scale on which the risks are described. For example, as described in LSS Report 12, the solid cancer excess relative risks (ERRs) associated with radiation exposure vary with sex (women greater than men) and age at exposure (younger survivors greater than older survivors), and there is some evidence that the ERR for those exposed as children has decreased with time since exposure. These results support the commonly-held view that women are more radiosensitive than men and that children are more radiosensitive than adults. However, the solid cancer risks in the LSS can be described equally well by a simple excess absolute rate (EAR) model in which the excess rates increase sharply with age but do not depend on sex or age at exposure. That suggests that in one (quite important) sense, men are not more sensitive than women and children are not more sensitive than adults to the carcinogenic effects of radiation

exposure. In addition, the EAR description indicates quite clearly that solid cancer excess rates for those exposed as children are increasing with time.

Descriptions of excess cancer risks in the LSS in terms of ERR or EAR models is useful. However, such models are quite abstract and, for many people, difficult to understand or interpret. There is a real need to develop alternative methods of presenting the results of analyses of the LSS data that provide accurate but more concrete and easily understood summaries of the impact of radiation on cancer risks in the LSS. In LSS Report 12 and other recent publications, we have taken several steps to address this problem, including the presentation of tables of observed and expected cases by dose group and other factors and through the use of lifetime risk estimates (by sex and age at exposure).

Low dose risks

The LSS data on cancer risks are often thought of as high-dose data. However, DS86 dose estimates for more than 40% to the LSS cohort members fall in the 5 to 200 mSv range with an additional 40% of the cohort having DS85 dose estimates of less than 5 mSv. Thus, the LSS is in some respects as large or larger than many of the individual occupational exposure cohorts used in studies of low dose (chronic exposure) risks. Thus, the LSS has some potential for the direct assessment of low-dose risks of acute radiation exposures. A standard, but poor, approach to the evaluation of low dose risks in the LSS or other studies has been to stratify the population into arbitrarily-defined dose groups and then carry out a series of tests to determine the first dose group for which the risk is significantly higher than the background rates. This approach lacks power and the results are generally misinterpreted in the sense that the failure to find a significant increase in risk is interpreted as evidence of no radiation effect (while in some circles any negative risk estimate, regardless of its statistical significance is interpreted as supporting hormesis). If this must be done, a better approach involves tests for trend using all of the data over the range from 0 to d with allowance for effect modification (e.g. by sex and age at exposure in relative risk models). When this method is applied to the Report 12 cancer mortality data, a significant trend is seen for the 0 – 50 mSv range. However, as noted in the report, it is quite plausible that this finding reflects the impact of small distance-related biases that distort the low risks. A more reasonable range over which there is support for a radiation-associated trend in cancer risks from both the solid cancer mortality and incidence data is 0 – 200 mSv.

A related question about low-dose risks concerns the shape of the dose-response function at low doses. This question is traditionally investigated through the use of linear, linear-quadratic, or threshold models. All of the these models place rather rigid constraints on the shape of the low-dose response and it is likely that the nature of the excess at higher doses (above 0.5 for example) determines the low-dose response. There is a need to develop more flexible methods for investigation of the shape of the dose-response function. A primary difficulty in this area arises because of the need to allow for the impact of effect modifiers on the excess risk. One approach to dealing with this problem that deserves attention involves the development of algorithms that combine non- or semi-parametric descriptions of the shape of the dose-response function (based for

example on LOESS or generalized additive models) with parametric models for the effect of factors such as sex, age at exposure, age, or time on the risk.

Modeling Issues

Over the past two decades, excess time-constant relative risk models have come to dominate descriptions of excess risks in the LSS and for radiation studies in general. However, as noted above and discussed in LSS Report 12 and elsewhere, simple descriptions in terms of age-dependent absolute (or relative) risks can lead to an important understanding of the nature of the radiation effects in the LSS and other radiation-exposed populations. RERF statisticians have played a leading role in the development and application of these more general models.

Consideration of excess absolute rate models leads naturally to the study of so-called "biologically-based" models for carcinogenesis. In recent years, various groups have applied such models to the LSS cancer mortality and incidence data. Such models are quite interesting and there is a need for RERF researchers to do more work in the application and assessment of such models to the LSS data. It is, in my view, particularly important for there to be more emphasis placed on the comparison of how well biologically-based and descriptive models describe the LSS data. Such comparisons could lead to ways to assess the adequacy and possibly provide insights that can help us reach a better understanding of the process of radiation carcinogenesis.

Looking ahead

Improvements in the Hiroshima and Nagasaki tumor registry and the development of standardized procedures for the conduct of site-specific incidence studies have made it possible for RERF to place increasing emphasis on incidence-based risk estimates. At present, we are analyzing and presenting separate results for mortality and incidence. Over the next few years, it will be important for us to develop procedures for a unified comprehensive picture of cancer risks based on incidence and mortality data. There are many questions about how this is to be accomplished, but it seems likely that site-specific results will rely more heavily on incidence data while general discussions of overall risk will involve both mortality and incidence findings.

Despite the importance of the continuing ABCC/RERF studies there are a number of key questions about radiation effects on cancer risks that cannot be answered or even addressed on the basis of the LSS data. In particular, questions related to dose-rate effects cannot be addressed using the ABCC/RERF data. However, it now appears that studies of cohorts of workers and the general population who received high radiation doses from chronic low-dose-rate exposures as a consequence of the operation of the Mayak plutonium production facility in the Southern Urals may be able to provide quantitative cancer risk estimates that will compliment those available from the LSS. It will be important for RERF scientists to work closely with the scientists involved in the risk assessment for the Mayak and Techa River cohort studies to develop a clear

understanding of the similarities and differences in risk estimates in these important radiation-exposed populations.

Much important information has been learned about radiation-exposure and cancer risks from studies of the LSS cohort. However, since about half of the survivors in the LSS and more than 90% of those exposed as children are still alive so even though 50 years have passed since these studies were begun it is certain that the ongoing follow-up of the survivors of the atomic bombings of Hiroshima and Nagasaki will continue to provide important new insights into radiation effects on cancer (and noncancer) risks for the next 25 years and beyond.

References

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Noncancer Mortality among Atomic-Bomb Survivors

Kiyohiko Mabuchi, Radiation Effects Research Foundation
ABCC 50th Anniversary Commemorative Symposium
Washington DC
June 13-14 1997

A statistically significant association between noncancer mortality and radiation doses among atomic bomb survivors has been documented for some time (1). A significant dose response is observed for mortality from stroke and diseases of the heart, respiratory system and digestive system. The latest LSS data provide further information on the noncancer excess risk and enable us to address several important issues related to the nature and magnitude of the risk. The issues that we consider here are: (i) the likelihood that the apparent radiation effects are due to bias or confounding; (ii) the dose-response models, linear or nonlinear, which should be used to estimate risks at low doses, say, <0.2 Sv; and (iii) the excess noncancer risks compared to the cancer risks.

Consideration of Possible Biases

Even though a dose-related excess risk of non-cancer mortality has been apparent in the LSS data for some time, this finding has been viewed with some skepticism for a number of reasons. First, the relative risk for noncancer is small compared to the relative risk for cancer. Second, there are no corroborating animal or human data on noncancer diseases associated with radiation exposure at dose levels received by the atomic-bomb survivors. Third, the apparent effect is seen for a broad range of disease categories with a variety of etiologic mechanisms. These points indeed raise suspicion regarding the causal nature of the association. Therefore, it is important that interpretation of these findings include a careful consideration of the possibility that bias or confounding might induce a spurious association between noncancer mortality and radiation dose in the LSS.

1. Death certificate misclassification of cancer deaths as noncancer will lead to a small, spurious noncancer radiation effect because of the established dose response for cancer. Comparison of LSS death certificate and autopsy data indicates that the probability of cancer misclassification is about 20%. Adjustments for this level of misclassification reduces the noncancer ERR by about 20% but the noncancer dose response remains highly significant (2). Thus, while such misclassification is a not negligible issue it is unlikely to be the primary explanation for the apparent noncancer risk. It should be also noted that the above correcting the non-cancer excess risks for the impact of death certificate misclassification *increases* the ERR/Sv for cancer by 10 to 15%.

2. The relative risk for noncancer for survivors with doses around 1 Sv is roughly 1.1. If such a small relative risk were seen in a simple comparison of exposed and unexposed groups it could easily be due to some, possibly unexplained, bias. However, in the LSS data there is a clear dose-related trend in the risk. Furthermore, the dose-distance relationship is such that a statistically significant dose response for noncancer mortality is seen even when attention is restricted to survivors who were between 900 and 1200 meters from the hypocenter. The estimated doses for these survivors range

from 0.35 to 5.9 Sv. It seems unlikely that the survivors in this narrow distance range would vary in socioeconomic, genetic, lifestyle or other characteristics to the extent to cause a spurious association between dose and mortality rates.

3. Over the years, several mail surveys have been conducted among the LSS subjects to obtain data on factors which could act as confounders. Those factors include education, occupation and other measures of socioeconomic status, and marital status, as well as smoking and alcohol intake. Some of these factors have been found to be significantly dose-related but the association is not strong enough to cause a confounding effect. Indeed, adjustment for smoking and other factors did not appreciably alter the ERR/Sv for noncancer.

4. Dose-related selection of the cohort by their survival of acute effects should also be considered. There does seem to be a "healthy survivors effect" in the cohort. Exposed individuals who survived until 1950, when the follow-up began, appear to have slightly lower death rates early in the follow-up. However, for selection-by-survival to explain the dose-related *increase* in noncancer mortality would require the opposite of this "healthy survivor effect". Those more likely to survive acute effects would have to have a smaller chance of living to an old age. This possibility cannot be ruled out but it does not seem very likely to be the explanation for the results.

Dose Response

As indicated above, there is clearly a dose-related gradient in noncancer mortality. The latest data also provide evidence that the excess risk is not exclusively derived from high doses. However, the precise shape of the dose response is still uncertain. The noncancer data are consistent with linear, linear-quadratic and quadratic models. They are also consistent with dose-response functions that have zero ERR up to around 0.5-1.0 Sv. The choice of a model, particularly a linear over non-linear model, has a large impact on estimating the risk in the low dose range of around 0.2–0.5 Sv. However, at this time, a broad range of dose-response functions provide comparable descriptions of the data.

Comparison to Cancer Risks

The ERR for noncancer is generally smaller than for cancer, but the higher noncancer background risk implies a large excess risk in terms of absolute numbers. For the follow-up period of 1950-1990, we estimate the number of excess deaths among the 14,645 deaths from noncancer causes except blood disease for those exposed to >0.005 Sv to be 125-250. The wide range reflects primarily uncertainties in the low-dose range. Since there are about 13,000 deaths in the range of 0.005-0.5 Sv, whether to use a linear or nonlinear model results in differences on the order of 100 excess deaths for this dose range. These estimates compare to 420 excess deaths from cancer including leukemia among the 4,863 deaths.

Further insights can be gained by the analysis of age-time patterns of risk. Using the linear model, an ERR for noncancer mortality is 0.11/Sv, not significantly dependent on age and sex, and this compares to an ERR for solid cancer for age at exposure of 30 years of 0.375/Sv for males and 0.774/Sv for females. In terms of EAR, however, the more rapidly increasing background risk with age for noncancer compared to cancer is

translated into higher EARs for noncancer at old ages. At young ages, the noncancer EAR is of the order of 10% of that for cancer; at older ages, the two EARs converge. Lifetime risks at high doses for those exposed at age 50 are twice that for cancer.

Future

Additional follow-up of the LSS cohort will provide data that will help resolve some of the uncertainties noted above. In particular, additional data may clarify the shape of the dose response, particularly at a low-dose range and thus improve risk estimation. Also, as with the cancer data, the pattern of noncancer risks among the survivors exposed during childhood and adolescence will become more certain with further follow-up.

Since the noncancer disease category is comprised of conditions of different etiologies and further work is needed to sort out heterogeneity that may be present in radiation response. Death certificate data, though essential for risk assessment, are less suited for studying specific noncancer diseases than morbidity data. As discussed in the following session in this symposium, the clinical follow-up program provides useful data on various noncancer endpoints. As with cancer risk assessment, our future task will be to develop a comprehensive approach to better understand the noncancer risk using both mortality and morbidity information.

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Radiation and Noncancer Diseases in the Atomic Bomb Survivors

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Epidemiologic studies of the late effects of exposure to atomic bomb radiations have spanned a of half of a century and have yielded a wealth of information. However, examinations of the relation between atomic-bomb radiation exposure and diseases other than cancer have been inconclusive in spite of long-term observations.

An exception is the report by Shimizu and coworkers of noncancer mortality in the Life Span Study in which a significant increase in mortality from noncancer diseases was found in association with atomic-bomb radiation exposure. Among the noncancer diseases, cardiovascular disease (CVD) and digestive diseases particularly showed excess mortality in the high-dose groups. For CVD, both stroke and heart diseases showed increased mortality at high doses. However, the excess relative risk for noncancer mortality was much smaller than that for cancer. Because of problems related to the accuracy of death certificate data, however, this finding must be confirmed by other studies, and a number of studies are now underway along these lines.

The association of atomic-bomb radiation and CVD was examined by incidence studies and prevalence studies of various endpoints of atherosclerosis, such as myocardial infarction, stroke, aortic arch calcification, isolated systolic hypertension, and pulse wave velocity in the Adult Health Study. Although the excess was small, all endpoints indicated an increase of CVD in the heavily-exposed group. Because of the consistency of the results, it is almost certain that CVD is increased among atomic-bomb survivors. However, all CVD risk factors associated with life style had not necessarily been adjusted and it is difficult to conclude that the increase of CVD among survivors was a direct effect of radiation.

Concerning the association between atomic-bomb radiation exposure and chronic liver diseases, the recent incidence study demonstrated a significant dose response. Both chronic hepatitis and cirrhosis were suggested as being associated with exposure. The possibility that the increased occurrence of chronic liver diseases among the survivors may be due to hepatitis virus infection can not be excluded, and the results of the ongoing studies on hepatitis B and C virus infection are awaited.

Recent studies have demonstrated almost certainly that uterine myoma is increased among atomic-bomb survivors. Uterine myoma presently can not be concluded as being a radiation effect, however, because of the lack of any such report from studies of other exposed populations. Further analyses including the role of confounding factors are needed to verify this

radiation effect. The relationship between atomic-bomb radiation exposure and parathyroid adenoma can now be said to have been established in view of the strong dose response, the agreement with results of studies of other populations and the high risk in the younger survivors. Future studies by molecular approaches are needed to determine the pathogenic mechanism. Among other benign tumors, a dose response has been demonstrated for the thyroid, stomach, and ovary. Although fewer studies have been conducted as compared with cancer, a clear association with radiation for various benign tumors is emerging.

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Major Studies and Future Plans, Nagasaki Laboratory

Masazumi Akahoshi
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Introduction

The relationship between the radiation exposure caused by the atomic bombings and carcinogenesis has been extensively studies from many aspects including epidemiologic studies and molecular biologic studies. While the effects of radiation exposure on noncancer diseases have not fully been elucidated, the recent developments in technology have made it possible to investigate the relationship between radiation exposure an noncancer diseases among atomic-bomb survivors, and then propose some future plans to elucidate the important findings obtained from these studies.

Thyroid Study

This study was conducted to elucidate the thyroid disease status for the Nagasaki Adult Health Study cohort from October 1984 to April 1987. 1978 subjects (752 men and 1226 women) whose Dosimetry System 1986 (DS 86(were available were included in the analysis. A high-resolution ultrasonic scanning technique developed for this study was used to detect structural abnormalities. The thyroid functions, antimicrosomal antibody and antityrogloblin antibody, were measured as well.

The results of this study revealed for the first time an increase in the prevalence of autoimmune hypothyroidism among atomic-bomb survivors, that is a significant ($p<0.05$) linear-quadratic and concave dose-response relationship was noted in the prevalence of antibody-positive spontaneous hypothyroidism. The dose to thyroid (SE) giving the maximum prevalence of antibody-positive spontaneous hypothyroidism was estimated to be 0.7 (0.2 Sv). Also, the prevalence of thyroid adenoma and thyroid nodules without histological diagnosis exhibited a significant ($p>0.01$) monotonic dose-response relationship.

Menopause study

The purpose of this study is to determine whether or not ionizing radiation affects menopause in the atomic-bomb survivors. In Nagasaki, the last menstrual period was recorded for all female subjects at each biennial examination and was defined as the time of menopause, when amenorrhea was observed for more than 12 months, except for pregnancy. 840 subjects with natural menopause were included in the analysis.

The results of this study revealed that the relative incidence of natural menopause increased nonlinearly with dose, suggesting that radiation accelerates the age at menopause. Taking

consideration of the fact that menopause occurs in all women, this result may support the hypothesis that radiation will accelerate aging.

Future plans

The Thyroid Study revealed an association between autoimmune disease and radiation exposure caused by the atomic bombings. Concerning the autoantibodies and immunogloblins, it has been reported that rheumatoid factors, Ig A and Ig M, were related to radiation exposure. In general autoimmune disorders increase with advancing of age. Therefore, the relationship between autoimmune diseases and radiation exposure should be studies extensively in the future because subjects of the Adult Health Study are becoming to be suffered from autoimmune diseases.

The estimated dose-response curve of the prevalence of antibody-positive spontaneous hypothyroidism is concave, reaching a maximum of about 0.7 at 0.2 Sv, and thus indicates the necessity for further studies on relatively low-dose radiation effects on thyroid disease.

In the Thyroid Study, 69 subjects having solid tumors without cancer and 105 subjects having cysts were identified. Follow-up study of these subjects is also necessary to examine whether or not they have developed thyroid cancer.

Although the precise mechanism(s) to explain why radiation accelerated the age at menopause are not known, the results of Menopause Study the hypothesis that radiation will accelerate aging. To elucidate the mechanism(s), "Longitudinal Study of Hormone Indicator of Menopause in Perimenopausal Female Atomic-bomb Survivors" has been started in 1993. In this study, approximately 300 female atomic-bomb survivors are followed at every 6 months. At each examination, menstruation status is recorded and blood samples are collected to measure estradiol and follicular stimulating hormone. When this study was started, the youngest age of Adult Health Study subjects was 48 years and we believed that this study was the last chance to study the basic mechanism(s) between atomic-bomb exposure and menopause. Many of the participants of this study are still on a pre-menopausal status and this study should be continued until all the participants experience menopause.

Studies of the molecular basis of cancer at RERF

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Radiation causes genetic and epigenetic changes in cells, which may be followed sometimes by the development of various kinds of cancers as a late effect. Epidemiologic studies revealed that, in general, cancer risks among atomic bomb survivors increase with increasing radiation dose. Research at RERF is primarily focused on the long-term epidemiologic studies of atomic-bomb survivors to ascertain morbidity and mortality in the exposed population, with specific investigations on health related effects. Clearly there is an important need for molecular and cellular studies aimed at revealing the underlying basis of this morbidity and mortality. Until recently, studies designed to ascertain changes at the molecular and cellular level have been limited.

Tumor development is considered to consist of multistep accumulation of adverse genetic and epigenetic events. Among those multistep genetic alterations, there may be specific genetic events uniquely associated with radiation carcinogenesis. We observed, following irradiation in various kinds of cells, induction of cancer-related genes such as H4-RET oncogene activation specific to papillary adenocarcinoma of the thyroid, or BCR-ABL fused gene specific to chronic myelogenous leukemia. The occurrence of either genetic change was not restricted by the type of cells. The results are in favor of the hypothesis that some radiation-induced cancers, including thyroid cancer and leukemia which are one of the high risk cancers among atomic-bomb survivors, might have developed when a growth advantage was obtained through the specific alteration of cancer-related genes by radiation exposure.

With this as background, it is reasonable to suspect that certain fingerprints in cancer-related genes remain in the cancer tissues of the atomic-bomb survivors. We have demonstrated that DNA or RNA extracted from old archival tissues is usable for molecular analyses by means of newly developed techniques. Even 40-year-old specimens preserved in formalin-fixed and paraffin-embedded blocks can be successfully analyzed after amplification by the polymerase chain reaction (PCR) or reverse transcription-PCR. High priority-studies will include cases showing the highest relative risks with sufficient number in the high-dose, histologically verified samples. Tissues will include thyroid, liver, skin, and breast. At present, p53 analysis of liver and skin samples from the atomic bomb survivors are well underway with suggestion of increased mutation frequency among the highly exposed. Preliminary results on the molecular analysis of HBV and HCV infection suggest differences in the infection rate between the exposed and unexposed populations. Although all molecular analyses are on-going, these can help to elucidate the molecular mechanisms of many clinical

conditions in which prospective studies are impractical due to the extended period of time required for the genesis of the disease or impossible due to the uniqueness of the study cohort as in case of the atomic-bomb survivors.

For the near term and for the future, collection of blood samples for cryopreservation from as many of the AHS participants as possible is in progress. The current number of the samples cryopreserved in the liquid nitrogen tanks is approximately 15000 from Hiroshima and Nagasaki. These cells will be an important resource for various planned and yet-to-be planned studies and functional cytologic and biologic analyses.

Atomic Bomb Survivor Dose Estimates

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Broadly accepted, reliable estimates of the radiation doses received by individual survivors are crucial to all aspects of the ABCC/RERF studies. Neither ABCC nor RERF have been directly involved in the development of the basic methods used to compute dose estimates for individual survivors, rather the basic dosimetry systems that have been used in these studies are developed and extensively reviewed by expert committees whose members are familiar will all aspects of nuclear weapons dosimetry and have access to the data necessary for the development of a dose estimation system. However ABCC devoted considerable resources to obtaining detailed shielding histories for virtually all of the proximal survivors in the Life Span Study (LSS) and other study groups.

The current dosimetry system (DS86) is the product of an extensive review of all aspects of the atomic bomb survivor dosimetry carried out by US and Japanese dosimetry experts during the 1980's. Once the basic DS86 system had been developed and approved by the senior dosimetry committees, RERF staff developed procedures for the computation of individual dose estimates. In the years after its initial introduction, the system was extended to provide DS86 dose estimates for Nagasaki factory workers and all LSS survivors who were more than 2,500 m from the hypocenter at the time of the bomb. At the present time individual, DS86 dose estimates are available for 86,572 of the 93,741 survivors in the LSS.

DS86 doses differ from the earlier T65D estimates in several important respects. In particular, DS86 unshielded free-in-air gamma kerma estimates in Hiroshima are slightly higher than the corresponding T65D values, while the new neutron kerma estimates are about one third of T65D estimates. For Nagasaki, the changes in unshielded kerma were in the same direction, but much smaller in magnitude. There are several other aspects of the DS86 dose estimates that had a significant impact on risk estimates. In particular, under DS86 the amount of shielding from gamma rays provided by a typical Japanese house is much greater than what had been assumed by T65D. In addition, the DS86 system provides estimates of the gamma and neutron doses received by 15 organs.

As is well known that risk estimates based on the DS86 system are somewhat greater than those based on the T65D estimates. This increase primarily reflects the changes in the amount of shielding provided by typical structures and various other factors including the use of organ doses instead of shielded kerma as the basis of the primary risk estimates.

The introduction of the new dosimetry system also lead to a careful reassessment of the likely magnitude and impact of random errors in individual survivor dose estimates on risk estimates. These investigations indicated that individual dose estimates are likely to have errors on the order of 35 to 40% and that making suitable allowance for the impact of these random errors results in 10 to 15% increases in risk estimates.

At the time that the DS86 system was made available to RERF there were still questions about the Hiroshima neutron dose estimates. Over the past decade a considerable effort has been made by both the US and Japanese dosimetry groups to obtain physical data that can be used to characterize and understand problems with the Hiroshima neutron dose estimates. At this time, it is clear that there are significant distance-related discrepancies between measured values and DS86 predictions of thermal neutron activation. The discrepancies are such that at distances at which there are appreciable numbers of survivors, i.e. beyond about 1000m from the hypocenter, measured thermal neutron activation in Hiroshima is greater than predicted by DS86. This discrepancy is about a factor of 10 at 1600m. While the US and Japanese dosimetry committees have considered this issue at great length, they have yet to come to any conclusion on what, if any, changes should be made to the Hiroshima neutron estimates. The Committees' concerns involve a lack of any plausible physical mechanism to explain the larger number of neutrons in Hiroshima, uncertainties about how to translate discrepancies in thermal neutron activation data to changes in neutron dose estimates, and the fact that direct application of the correction suggested by the neutron measurements leads to inconsistencies between measurements and predictions for other aspects of the DS86 system.

Despite the dosimetry committees' reluctance to suggest any modification in the neutron doses based on the activation measurement data, there have been a number of discussions about the impact of changes in neutron doses. Our analyses of the LSS cancer mortality data suggest that, under a variety of assumptions about the neutron RBE changing the Hiroshima neutron doses to reflect the discrepancies suggested by the activation data has a relatively small impact on low dose gamma risk estimates derived from the LSS data.

Hiroshima neutron dose is not the only area in which there is evidence of problems with DS86. It has been suggested that gamma dose estimates may need to be increased by about 10%. In addition, chromosome aberration data for Nagasaki factory workers suggest that DS86 overestimates the doses for Nagasaki factory workers by about 50%. This group is important because factory workers constitute more than 30% of the Nagasaki survivors with dose estimates in the 0.5 to 2 Gy range and because of the (over) emphasis on inter-city comparisons in the efforts to make inferences about the neutron RBE from the LSS data.

Even though the changes in risk estimates may not be great (though that is not certain), in view of the various questions that have been raised about the DS86 estimates it is hoped that the US and Japanese dosimetry committees can soon provide RERF with an updated version of DS86.

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Cytogenetic Information from A-bomb survivors -- Validation for Individual Dose Estimation and Future Application to Estimating Dose Errors in DS86.

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Since the late 1960s, Dr. Awa and his colleagues have conducted a large-scale cytogenetic survey of A-bomb survivors. Their initial finding was that the dose response was close to being linear for Hiroshima survivors and curvilinear for Nagasaki survivors when cytogenetic data were regressed with the T65D dose. Also, the Hiroshima curve was higher than the Nagasaki curve. These results were interpreted as due to a larger fraction of neutrons released from the Hiroshima bomb. Since 1986, the current dosimetry system, DS86, has been introduced and the city differences regarding the neutron component became much smaller than in T65D. Whereas both Hiroshima and Nagasaki curves became curvilinear, the tendency that the Hiroshima curve was higher than the Nagasaki curve remained as a factor of nearly 1.5.

Another consistent finding was that the chromosome aberration frequencies dispersed quite extensively, much more than expected from simple statistical fluctuation (termed as overdispersion). Such a large variation may be attributable, at least theoretically, to biological factors such as individual differences in radiation sensitivity, effects of age at the time of exposure, etc., but also may be due to dose assignment errors. To clarify the issue, additional biodosimetric indicators have been vigorously sought. The mutation frequency of various blood cells was once thought to be a potential quantitative indicator of radiation exposure, but recent scrutiny has revealed that, among a half-dozen assays examined, none was as useful as cytogenetic information.

Recently, electron spin resonance (ESR) of tooth enamel has been further developed and appears to be a promising new tool for retrospective dosimetry. We have conducted ESR measurements of 100 teeth donated from 69 Hiroshima survivors and the results were compared with cytogenetic data of the tooth donors. We found that the cytogenetic data correlated more closely to the ESR-estimated dose than to the DS86-estimated dose. Further, frequencies of translocation (one of the cytogenetic markers of radiation exposure known to persist over years after the exposure) were very close to what we would expect from in vitro irradiation experiments.

The close one-to-one correlation between tooth enamel ESR and chromosome aberrrations leads us to be convinced that the overdispersed cytogenetic data are a valuable source of information to assess possible errors in individual doses estimated by DS86. We found that, although the average frequencies of chromosome aberrations in

Nagasaki survivors were nearly two-thirds of those seen in Hiroshima survivors, the city difference largely diminished among those who were in Japanese houses at the time of the bombings. Subsequent analyses revealed that the lower average frequencies of Nagasaki survivors were largely due to factory workers whose DS86- estimated doses appear to be overestimated by a factor of nearly 2.

Although tooth enamel ESR is a very attractive method for retrospective dosimetry, the critical disadvantage is that extracted teeth are required for the measurement but are only occasionally available. In contrast, cytogenetic testing requires only 2 ml of blood which is available from most survivors. Consequently, cytogenetic testing is superior for a large-scale survey and ESR data will serve as validation of the cytogenetic data.

Currently, fluorescence in situ hybridization (FISH) has been adopted to measure translocation frequencies. FISH has been regarded as the most objective way to score such aberrations. It is time now to shift our focus to look at systematic biases as well as random errors associated with DS86 estimates. In the meantime, only cytogenetic data can provide the key information. Examination of as many survivors as possible whose DS86 estimates exceed 0.5 Sv, for example, should be undertaken to accomplish reassessment of the radiation-induced cancer risks.

Radiation dose reconstruction of atomic bomb survivors by Japanese group

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After the determination of DS86 in 1987, Japanese committee continued measurements of exposed samples in Hiroshima and Nagasaki. We collected and measured rock and concrete samples to determine specific activities of ^{152}Eu and ^{60}Co for neutron dose evaluation and did tiles and roof tiles to observe thermoluminescence for gamma-ray dosimetry. As a result of these studies we find out that there are some discrepancies between measured data and DS86 both in neutrons and gamma rays in Hiroshima.

Most large discrepancy is seen in the neutron dose in Hiroshima. At ground zero data are 2-3 times lower than DS86. They have greater values more than 1 km ground range and, at 1.5 km ground range, seem to be even several times higher than DS86.

In the case of gamma rays in Hiroshima, data are almost agree with DS86. However, they seem a little bit lower near ground zero and higher at 2 km ground range. The discrepancy is small but it have the same trend as neutrons.

We are also analyzing the data to explain these discrepancies. For the case of neutrons, at the ground range within 1 km, it can be explained by a leakage of fast neutrons from the atomic bomb body. On the other hand at the ground range more than 1 km, its discrepancy is very high as if they are transporting through air without any interaction.

The discrepancy of the gamma rays are not large. However we are interested in it since (1) it may correspond to the neutron discrepancy and that (2) increases low dose side for example from 10 cGy to 17 cGy. The latter will relate to the discussions of threshold of the cancer induction and so on.

In the case of Nagasaki, there are questions in neutron activation data. There are two data groups which contradict each other. One of the group is Dr. Shizuma's recent data and Dr. Hashizume's old data. Both cobalt activation. They show discrepancy from DS86 as is in Hiroshima. The other is Dr. Nakanishi's unpublished europium activation data and Dr. Straume's chlorine activation data. Both show no difference with DS86. The contradiction with the both data groups must be solved since it will

decide whether the problem is in transport calculations or the other problems e.g. the source neutron spectrum.

Our future study is to confirm (1) neutron activation data at longer distances in Hiroshima and (2) those in Nagasaki's. Actually we are doing intercomparison study with the three groups such as Drs. Nakanishi, Straume and Shizuma for these purposes. For both cases it will be necessary to solve the mechanism of their discrepancy. We are also trying to analyze problems in the source term of Hiroshima. One of our calculation of "leakage of fast neutrons" can explain within 1 km ground range data, however, cannot more than 1 km. Our final goal is to determine a new correct atomic bomb survivor's doses as DS86.

DNA Analysis of Children of Atomic Bomb Survivors

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Extensive studies of the children (F1) of A-bomb survivors have thus far yielded no statistically significant increases in genetic effects compared to findings in a control population. In our new studies to screen the children for germline mutations at the DNA/RNA level, we have introduced several techniques and improved them for screening purposes, and planned to establish cell lines from B-lymphocytes from 1,000 (500 exposed and 500 control) families consisting of father-mother-child trios. Cell lines, untransformed lymphocytes and granulocytes from over 900 families are preserved in liquid nitrogen as sources for the future studies.

In 1991, the Human Germline Mutagenesis Workshop recommended various targets and techniques for detecting germline mutations and, suggested that pilot studies be undertaken to examine the efficiency of the techniques using 100 families from the cell line project. We selected 50 families, containing 64 children, including the most heavily exposed survivors (1.8 Sv mean gonadal dose) along with 50 control families with 60 children. We are now determining whether deletion/insertion/rearrangement (D/I/R) types of mutations, believed to predominate among radiation induced mutations, exist in higher frequency in the exposed group for various repetitive sequences and single copy sequences.

As repetitive sequences, we examined six minisatellite loci, DNA fingerprints, and six microsatellite loci from 124 children and detected 28, 24, and 6 mutations, respectively. However, these germ cell mutations showed no evidence of being induced by radiation. We improved resolution of bands in the DNA fingerprints, and the children are being reexamined with the improved technique. In addition, 100 (50 exposed and 50 control) new families will be screened for mutations in these repetitive sequences.

In screening for D/I/R mutations in single copy sequences, we improved the two-dimensional gel electrophoresis (2-DE) of the DNA approach of Hatada et al. (1991). We used *Not*I as one of three restriction enzymes to digest DNA. The *Not*I sites, which are frequent in unmethylated "CpG islands," were labeled with ^{32}P. This strategy is thought to assure that a high proportion of visualized fragments (spots) originate from active genes. Because a fresh mutation would usually be detected in heterozygotes containing one normal and one mutated allele, a quantitative analysis for a 50% decrease in spot intensity is required. For the quantitative analysis of 2,000 spots on a gel from a human genomic DNA digest, we employed computer algorithms developed by Drs. Neel and Hanash of the University of Michigan in a cooperative study. Results of a preliminary study on three trios showed that this technique can distinguish the one-copy spots from the two-copy spots.

In a study on mice to validate the 2-DE approach for detection of radiation-induced germinal mutations and to obtain information on the number of children of survivors required for statistically significant results, F1-mice (BALB/c) derived from spermatogonia irradiated with 5 Gy and 3 Gy (X-ray) and control F1-mice are being examined. Quantitative image analysis showed that approximately 500 spots per sample per gel are suitable for detection of the D/I/R mutations. Preliminary results show that two mutations were detected among a total of 45,264 spots from the 5-Gy-exposed group (89 gels) and no mutations were detected among 31,859 spots from the control group (61 gels). By using the method that permits target cloning of DNA spots on the 2-DE gel, mutant fragments are being characterized. DNA samples from the 3-Gy-exposed group are being examined.

For the analysis of human DNA, we are readjusting experimental and analytical conditions using information obtained from the mouse study. As soon as this is completed, screening on the DNA from the original 100 families with the 2-DE technique will be carried out.

What the Two-Dimensional DNA Technique Can Contribute to an Understanding of the Genetic Effects of the Atomic Bombs

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This is an important juncture in the studies of the potential genetic effects of the atomic bomb explosions. It appears that we are in a period of major reevaluation of the magnitude of the genetic risks created by the ionizing radiation released by the bombs. As you are aware, two cohorts of children are now in place, the one consisting of 31,150 children one or both of whose parents are classified as exposed to the radiation of the atomic bombs, the other of 41,066 suitably matched control children whose parents were not exposed. These cohorts have been studied with respect to viability at birth; congenital malformation; sex of child; survival up to the present time; cancer up to the present time; physical development at birth, at nine months, and during the Middle School years; cytogenetic abnormality; and electrophoretic or functional defects in a battery of some 30 serum proteins or erythrocyte enzymes. For none of these indicators has the endpoint been found to be significantly related to the parental radiation exposure. However, for those indicators where a regression analysis was possible, the net regression was slightly positive (Neel et al. 1990). On the assumption that the small regression term reflected a genetic effect, and that the contribution of spontaneous mutation each generation to each of these indicators could be estimated, it was possible in 1990 to reach a rough estimate of the zygotic doubling dose of radiation, i.e., the amount of radiation that will produce the same quantity and kind of mutations as will occur spontaneously each generation. This estimate was in the neighborhood of 2 Sv equivalents. The data excluded at the 95% confidence level a doubling dose of 1 Sv equivalent, but in the absence of statistical significance, no upper bound could be placed on the estimate. At the time, this estimate appeared higher than the consensus estimate of .4-.5 Gy, based on the extensive mouse experiments carried out at various laboratories but especially the Oak Ridge National Laboratory in this country. However, a reevaluation of the murine data by Neel and Lewis (1990) plus the discovery of some serious flaws in how the Russells' data have been used to generate doubling doses (Selby 1996) suggest the mouse estimate has been much too low, and the two doubling dose estimates, human and murine, are now in reasonable agreement.

There are reasons to believe on the basis of the Japanese data, that even this relatively high estimate of the doubling dose may be conservative. First, the assumptions that went into the estimate were cautious as regards the contribution of spontaneous mutation to the end points. Secondly, the socioeconomic status of the exposed survivors was somewhat lower than that of the controls in the decade following the bombing (Kato et al. 1966). This fact could have inflated stillbirth, neonatal, and childhood death rates in the children of exposed and, unavoidably treated as a radiation effect, have depressed this estimate of the doubling dose. Third, it appears that the neutron component in the radiation spectrum of the bombs may have been underestimated. Since for most genetic endpoints neutrons have an RBE in the neighborhood of 20, any revision upward in the estimation of the neutron component would of course increase the doubling dose estimate in direct proportion to the increase.

This is, then, an interesting time in the evolution of genetic thinking regarding radiation risks and, given limited resources, the future genetic activities at RERF, clearly of great important to this evolving picture, must be planned with the utmost of care. Drs. Satoh and

Mabuchi have presented an overall picture of the proposed future genetic studies at RERF. I will speak in some detail to just one of these, the proposed 2-D DNA studies.

This effort thus far has involved a fusion of DNA technologies brought up at RERF and computer technologies developed in the Department of Human Genetics at the University of Michigan. In this approach, genomic DNA is enzymatically digested, a subset of the resulting fragments labeled with ^{32}P, and then the digest spread out in two dimensions by the technique of electrophoresis. The position of the resulting labeled fragments, ranging in size from approximately .5 to 10 kb, are visualized by autoradiography or a phosphor image, as shown on the slide. One visualizes about 2000 fragments, a considerable subset of which — of the order of 500 fragments — are sufficiently reproducible that they can be analyzed for both qualitative and quantitative genetic variation. At the moment, the nucleotide composition of the majority of these fragments is unknown, but it is anticipated that using the techniques of molecular genetics, the identities of most of the fragments and the nature of the variation can be established. The observed variation is thought to derive either from nucleotide substitutions involving the cutting sites of the enzymes employed or insertions, deletions, or inversions involving the DNA fragments. This method should be especially efficient in detecting the deletion-type damage which is the chief genetic product of radiation exposures, although detailed studies at the molecular level will be necessary to verify any presumed deletion mutation. Mutations are characterized by the appearance in the child's gel of a variant not present in either parent. The scoring of these gels is enormously facilitated by the use of computer algorithms that we have developed at Michigan over the years. A pilot study involving the application of the technology to the cell lines Dr. Satoh has described is now underway, and this presentation will describe some of the early results (cf. Asakawa et al. 1994, 1995; Kuick et al. 1995, 1996).

In closing, let me emphasize that if the 2-D DNA program goes forward on an adequate scale, we're looking at a major effort with probably relatively little return in the way of mutations. Even this approach on a large scale may not yield statistically significant differences between the children of controls and exposed. However, non-significant differences between the two data sets still are useful in evaluating genetic sensitivities and would be an important step in dispelling fears about hidden recessive mutations that will crop up generations from now. Furthermore — and this is why I emphasized past studies — these data can and must be taken in conjunction with all the data of the past, to create a rounded picture of the genetic legacy of the bombs.

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F_1 Health Survey

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Studies of genetic effects have been the primary focus of the ABCC and RERF research program. A variety of different approaches have been used to estimate genetic damage from parental exposure to atomic bomb radiation. The earliest, and most extensive genetic studies concerned congenital abnormalities and still births among some 77,000 individuals. These were followed by studies of reciprocal translocations conducted in 16,000 children, the screening for protein alterations by one-dimensional electrophoretic gels involving 23,000 children and measurements of enzyme activity were carried out among 10,000 individuals. The mortality follow-up of 76,000 individuals (F_1 Cohort) has been in progress. The cohort is now extended to include a total of some 88,000 individuals. Despite these extensive efforts, none of the genetic studies thus far have provided unequivocal evidence on genetic damage transmitted from exposed parents.

There are, however, a few genetic issues that remain to be addressed. The past few years have witnessed unprecedented progress in understanding of the molecular basis for human genetic diseases, particularly polygenes/multifactorial diseases. Thus, the Human Germline Mutagenesis Workshop held at RERF in 1991 recommended that further medical evaluations of the F1 cohort be considered. The early genetic program was designed to identify pregnancy outcomes and congenital abnormalities that are observable during later months of pregnancy and soon after birth. There has not been any program to search systematically for those abnormalities that are detectable many years after birth and other inherited - both mendelian and multifactorial - diseases that are manifested later in life. Multifactorial diseases, such as hypertension, circulatory diseases and diabetes, have such high prevalence in adult life that these present by far the largest proportion of inherited disabilities. Furthermore, there is widespread concern over the adverse genetic consequences of radiation exposure, and this concern apparently causes considerable apprehension and misconception among the atomic bomb survivors and other populations exposed to radiation.

The Blue Ribbon Panel, convened in 1996 to evaluate the RERF research program, recommended that "consideration be given to further investigation into the health of the offspring (F_1 cohort) since it may yield valuable information on genetic effects, especially when conducted together with research using the new genetic techniques." In response to this recommendation, RERF began to prepare plans for the conduct of a preliminary study to assess the feasibility of a health survey among the F_1. The preliminary study includes two parts: a mail survey in a sample of the F_1 cohort and clinical examination in a smaller sample of F_1 adults.

The planned mail survey will be conducted in some 39,000 members of the F1 cohort and will obtain information on socioeconomic and lifestyle factors (such as smoking and alcohol intake) which will be used in future analyses of disease risks. Since many of the F1 cohort members have migrated out of Hiroshima and Nagasaki, information on their whereabouts obtained from this survey will be essential in using the tumor registry-based cancer incidence data for cancer risk estimation. Our original plan was to include questions on health outcomes. However, the Scientific Council has recommended that health outcome questions be avoided because of the concern that a potential bias may be introduced by self-reporting. Other epidemiologists and researchers have indicated that such a concern is unwarranted because the subjects are not aware of their radiation exposure doses even though some of them may be cognizant whether their parents were exposed to the bombs.

The clinical pilot study will be limited to about 600 subjects who live in the Adult Health Study contact areas and who have been examined as part of previous RERF genetic studies. The subjects will be sampled so that as many people with heavily exposed parents as possible will be included together with balanced numbers of people with less heavily or negligibly exposed parents. The subjects will receive a comprehensive AHS examination and be requested to provide blood samples for future biological assays.

Currently, 94% of the F_1 cohort members are alive and their mean age is about 35. While the prevalence of multifactorial diseases is still low, it will rise sharply as people reach older ages. The lifetime prevalence of multifactorial diseases is estimated to be of the order of 60-70%. Risk estimation for multifactorial diseases has hindered by the lack of knowledge of their biological basis and the limited epidemiological information available. The long-standing genetics program at RERF is and will remain the singular study worldwide on the genetic effects of radiation in humans. We would be negligent if we did not attempt to investigate this issue or at least to lay foundations for future work.

Training and Collaboration Programs at ABCC/RERF

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Historical overview

A number of research training and collaboration programs have been conducted at ABCC/RERF. The aim of these programs is two-fold. One is purely an educational purpose; i.e., RERF offers an opportunity for scientists from developing countries to learn various techniques and the know-how for radiation-related research and for risk evaluation of various radiation hazards. The other is to train young scientists either at RERF or other institutions and universities for mutual benefit as well as for recruitment of young scientists to RERF.

Over the years, we have received many scientific trainees at RERF based upon agreements between RERF and other organizations. Among these, the following are some of the representative training programs: (a) US-NCI cancer fellow training program (1972-1977); (b) China-RERF training program (1980-1991); (c) exchange program with the University of Washington (1979-1986); (d) Chelyabinsk study (Ural Research Center of Radiation Medicine, URCRM) (1992-1995); and (e) Mayak study (1995). A program considered to be considered most successful was the one conducted between RERF and University of Washington (Department of Statistics) in which RERF invited faculty members and students to the Departments of Statistics and Epidemiology at RERF to engage in the utilization and analysis of the RERF data in collaboration with RERF statisticians and epidemiologists.

Recently, requests from both HICARE (Hiroshima International Council for Health Care of the Radiation-exposed) and NASHIM (Nagasaki Association for Hibakushas' Medical Care) have been increasing for training physicians and radiation biologists for medical care and risk evaluation mostly from the former Soviet Union. To this extent, RERF has played an important role in conducting such a training program to deal with the Chernobyl nuclear power plant accident.

Future aspects

Since important biological and pathological resources are available at RERF, there will be an increasing need for training and international collaboration programs and for future research activity. Expanded training program's at RERF should include institutions and universities not only from the US and Japan but also from the countries in the European community. It should be stressed here that such programs should be mutually beneficial and directed towards research mainly in the fields of epidemiology and statistics.

We have heard about recent progress in the promotion of the RERF training program by collaboration with various universities and the National Institutes of Health in the United States. Today, Dr. Wald from the University of Pittsburgh and other speakers will discuss training programs recently developed in their organizations. We will also hear from Dr. Sinnaeve about possibilities for collaborations with the European community. It will be important for RERF to work with the institutions in order to develop the best possilbe collaborations for training and research.

A New Postdoctoral Fellowship Program in the Radiation Sciences

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ABCC/RERF 50th Anniversary Commemorative Symposium
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This presentation will describe the new Postdoctoral Fellowship Program in the Radiation Sciences at the Graduate School of Public Health (GSPH) at the University of Pittsburgh. This Program, although developed in response to the stated needs of the US Department of Energy (DOE), is a logical extension of the multidisciplinary GSPH graduate training and research program focused on the health aspects of nuclear technology that began as a formal academic activity in 1958. Our primary objective in establishing the Postdoctoral Fellowship program is to replenish the currently declining supply of U.S. scientists and physicians with sufficient comprehensive training and clinical and/or research expertise in the radiation health sciences to insure the health and safety of radiation workers and the public.

Since our goal is to train multidisciplinary radiation scientists, we are enrolling graduates of doctoral programs, which tend to be multidisciplinary and narrowly focused, and broadening their outlook and skills to the extent needed to function well in meeting the demands of the complex environment of radiation health research and practice. To do so, we have designed a Postdoctoral Program to identify and recruit the best Fellowship candidates with scientific or medical doctoral degrees, and to provide an individualized, intensive and focused two-year postdoctoral training curriculum.

The Program provides a first year of comprehensive classroom instruction, laboratory rotation and research, seminars with invited outside speakers, journal clubs and a special workshop in radiation epidemiology. This is followed by a second year at a field site of DOE interest, such as RERF in Japan, Chernobyl's Baltic cleanup workers, Mayak nuclear facility workers in Chelyabinsk, Russia, domestic DOE post-Cold War cleanup projects and the DOE's National Laboratories. Selection of the academic and field experiences from among the many available to us are based on the skills, needs and interests of the individual Fellow. A competitive stipend and travel expenses are provided for the Fellows.

The University is also organizing and supporting an annual Symposium in Radiation Sciences to bring together experts in selected key areas of radiobiology and radiation health. This is to give Fellows an opportunity to interact personally with the leading experts from academia, government, and industry.

The Program faculty in the Department of Environmental and Occupational Health represents a broad range of relevant disciplines, with established academic strengths and expertise in

educating pre- and postdoctoral scientific and medical trainees to conduct research and address radiation health problems requiring a knowledge of health physics, radiobiology, radiation epidemiology, toxicology of radiation/chemical exposures, occupational and environmental medicine, and health-risk assessment. It benefits from the strong departmental teaching, research and clinical collaborations already in place between specialists in Occupational and Environmental Health, including Occupational and Environmental medicine and Radiation Health. The Program faculty also includes members of the University of Pittsburgh's academic Departments of Biostatistics, Epidemiology, Health Services Administration, and Human Genetics in GSPH; and the Departments of Radiation Oncology and Radiology in the School of Medicine; as well as staff members of the University's Offices of Environmental Health and Safety and of Radiation Safety.

Project administration and academic oversight are provided by an Executive Committee including Drs. Niel Wald (Radiation Medicine), William Bigbee (Radiobiology), Gregg Claycamp (Health Physics) and William Gauss (Occupational Medicine). An External Advisory Committee to critique the Program is chaired by Dr. Arthur C. Upton and includes Drs. Bryce D. Breitenstein, Jr., Robert W. Miller, John W. Poston, and William J. Schull.

In summary, this broadly based postdoctoral training and research Fellowship Program is designed to recruit and train a critical mass of scientists and physicians to address the programmatic needs of the DOE and to provide the U.S. and the international community with the personnel able to conduct radiation-related research and health care to facilitate the generation and support of rational and scientific based public policy and regulation in Radiation Health.

RERF Dosimetry: Challenges Ahead

Tore Straume, University of Utah
ABCC 50th Anniversary Commemorative Symposium,
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The dosimetry for A-bomb survivors has seen several improvements during the past 40 years. As dosimetry capabilities improved, the doses have become more accurate taking into account intervening shielding and more useful by providing doses to specific organs. However, despite the successes of the past, there are still major challenges ahead for RERF dosimetry. For example, a large discrepancy is evident in the Hiroshima neutron dosimetry, substantial uncertainties remain in the doses to Nagasaki factory workers, and emerging physical and biological technologies should be explored for possible RERF dosimetry applications.

THE NEUTRON PROBLEM

The discrepancy between measured thermal neutron activation and calculations based on DS86 was suggested in the mid 1980's. However, not until additional activation measurements were made did it become clear that the discrepancy was real and systematic reaching measured-to-calculated ratios on the order of 10 at 1500 m. It was also recognized in the DS86 report that thermal neutrons *per se* did not contribute much to the dose. That is, the neutron dose from a fission spectrum is principally from the high energies. However, at the large distances of 1000 m or more thermal neutron activation should be an approximate correlate for neutron dose because a substantial fraction of the thermal neutrons in, e.g., a concrete wall, were produced from higher-energy neutrons that slowed down by multiple collisions in the local environment of the sample.

Measurements of high-energy neutrons were made in Hiroshima shortly after the bombing in 1945. Those measurements involved the detection of beta-rays emitted from ^{32}P produced via the reaction $^{32}S(n,p)^{32}P$. This reaction has a threshold of about 3 MeV and the product has a half life of about 14 days. The measurements were made using 1930's vintage detection systems and the short half life of ^{32}P has prevented subsequent validation of those early measurements.

Since publication of the DS86 report, there have been considerable efforts underway to resolve the neutron discrepancy in Hiroshima. The first concern was to verify the prior thermal neutron activation measurements that suggested a discrepancy. A large number of thermal neutron activation measurements were made by laboratories in the US and Japan using various isotopes and methods. The measurements demonstrated a clear discrepancy for thermal neutron activation in Hiroshima. The next concern was to determine whether the disagreement between thermal neutron activation measurements and DS86 calculations was the result of problems with the air transport calculations used in the DS86 system or with an inadequate understanding of the bomb explosion itself, i.e., the source term. To deal with this concern, several efforts were undertaken including measurements of the neutron cross section for nitrogen, thermal neutron activation measurements at Nagasaki, and a field experiment at the Army Pulsed Radiation Facility in Aberdeen, MD. The neutron cross-section measurements demonstrated some differences with the cross-section data used in DS86 but the differences were not large enough to explain the discrepancy in Hiroshima. The ^{36}Cl activation measurements in concrete cores from Nagasaki showed good agreement with the DS86 calculations. The Aberdeen field measurements, which included both ^{36}Cl in salt and BF3 detectors, demonstrated good agreement with DS86-type calculations for thermal neutrons. In addition to these contemporary measurements, DS86-type calculations were made for weapons tests in Nevada and compared with available measurement results for thermal and fast neutron activation. Again, good agreement was obtained. These and other studies lead to the conclusion that the discrepancy between DS86 calculations and measured neutron activation in Hiroshima is not due to a problem with air transport, but rather is due to a problem with the DS86 neutron source-term.

As a result of these studies, the focus is now on techniques that may be used to characterize the Hiroshima neutron source term. Initial "what if" analyses by the US Working Group indicated that there were no simple source term fixes as long as all of the measurement data were considered equally valid. For example, no reasonable fission neutron source was found that could explain the ^{32}P, thermal neutron, and TLD measurement data simultaneously. Adding more fission-spectrum neutrons to the Hiroshima source improved the thermal neutron comparison but destroyed the comparison for ^{32}P. Unfortunately, the TLD data did not provide a strong discriminator. In contrast to the thermal neutron measurements that have been made independently by several groups and techniques, the ^{32}P measurements were made with 1930's vintage equipment and are the only *in situ* measurements that have not been independently validated during the Dose Reassessment Program. The focus is therefore on confirming or refuting the old ^{32}P measurements.

An extensive search has been performed for activation reactions with neutron-energy thresholds in the 1-MeV range and with products that have half lives sufficiently long to be measurable today, more than 50 years after the bombings. Only a handful of reactions were identified that could potentially be used in Hiroshima, and the best-candidate reaction appears to be $^{63}Cu(n,p)^{63}Ni$. The half life of ^{63}Ni is 100 years and the neutron cross section of ^{63}Cu has a threshold of about 1 MeV. Furthermore, samples of copper are available in Hiroshima and more should hopefully be obtainable when an all-out search is undertaken. Calculations based on DS86 indicate that in 1997, the amount of bomb-induced ^{63}Ni present in a copper sample from near the Hiroshima hypocenter would be about 1.5×10^7 atoms g^{-1}. During the past year we have demonstrated that accelerator mass spectrometry (AMS) in combination with ultra-pure separation of nickel from copper can be used to measure such low concentration levels of ^{63}Ni. The present capability permits the measurement of ^{63}Ni induced by Hiroshima neutrons to about 500 m from the hypocenter. Measurements at much larger distances appear feasible based on our recent studies involving modifications that further discriminate the copper isobar. Needed work:

- Extend ^{63}Ni measurement capability to at least 1500 m in Hiroshima.
- Measure the copper samples now available at 1310 and 1470 m in Hiroshima.
- Obtain more copper samples from Hiroshima (and Nagasaki).
- Perform DS86 calculations to compare with measurements taking into account local environment of the sample and elemental composition.

In addition to solving the fast neutron problem, it is also necessary to reduce the uncertainties in the thermal neutron data in Hiroshima (and Nagasaki). This is important because it is unlikely that a sufficient number of copper samples will be obtained at relevant distances to reconstruct a complete fast-neutron profile for Hiroshima. Thus, an accurate full-range profile of thermal neutron measurements will be required to supplement the fast neutron data. Ideally, these thermal activation measurements would be made in deep concrete cores such that each sample would have its own background measurement. Also, such samples may provide some fast neutron information by comparing measured ^{36}Cl profiles in cores with Monte Carlo calculations to infer an effective neutron energy spectrum. Needed work:

- Complete the ^{36}Cl and ^{152}Eu profiles from near the hypocenters to more than 2000 m at Hiroshima (and Nagasaki).
- Perform direct (on the same samples) intercomparisons between the ^{36}Cl and ^{152}Eu measurement labs.

• Perform DS86 calculations to compare with measurements taking into account local environment of the sample and elemental composition.

Our expectation is that the above recommended work will provide the Dosimetry Committees with the neutron measurement data required to develop a revised dosimetry system that would hopefully be consistent with all of the measurements.

NAGASAKI FACTORY WORKERS

A large fraction of the Nagasaki survivor cohort at doses in the 1-Sv range were inside various Mitsubishi factory buildings. In the T65D dosimetry system, transmission factors (TFs) of 1.0 were assigned to these buildings and in DS86 TFs in the 0.8 to 0.9 range were assigned. The problem is that there were large machinery and other equipment in the factories that could have shielded the workers resulting in a very complex shielding situation. This possibility is supported by cytogenetic evaluations at RERF that suggest that DS86 overestimates the doses for these workers by perhaps 50% (Preston, this symposium). Needed work:

• RERF should do an all out effort to collect teeth and blood samples from these survivors. Also, if possible, teeth should be taken at autopsy.

• After further validation and calibration of electron paramagnetic resonance (EPR) and fluorescence *in situ* hybridization (FISH) biodosimetry (see below), RERF should perform biodosimetry measurements on this cohort and compare with the physical dosimetry. Consideration should be given to dose assignments based on the biodosimetry results. However, such assignments should be made with caution and only after expert evaluation of all relevant parameters.

BIODOSIMETRY

New technologies such as EPR spectrometry in tooth enamel and FISH to detect stable chromosome translocations in blood lymphocytes have emerged that appear promising for RERF dosimetry applications. Of course, these methods can not replace the physical dosimetry system because more than half of the survivors have died and samples were not generally collected from them. However, they may provide key dosimetry information to supplement the official dosimetry system. For example, to reduce uncertainties in dosimetry for difficult shielding cases, to evaluate the distribution of individual doses within dose cohorts, and to provide independent doses that can be compared with the physical dosimetry system. Although these biodosimetry techniques appear very promising, there are some serious challenges to confident applications at RERF.

The very long time since exposure of the A-bomb survivors means that there is an extraordinary requirement for signal stability. It is known that the temporal stability of the chromosome translocation frequency can be affected by non-uniform distribution of dose as well as by acute doses above about 2.5 to 3 Sv. For non-uniform exposures, the translocation frequency will decrease due to repopulation from unexposed stem cells and for high acute doses such as received by many of the survivors in Hiroshima and Nagasaki the chance is great that a cell with a translocation will also contain an unstable aberration. A question that RERF must answer is how much instability would be expected for the doses and dose distributions received by typical survivors?

The very different locations in the body of teeth and blood stem cells will likely result in differences due simply to their relative positions receiving somewhat different doses. This and several other technical and dosimetry-related issues will have to be taken into account in the design of biodosimetry studies and in the interpretation of results. Also, the Hiroshima and Nagasaki gamma rays were of unusually high energies compared with the common gamma-ray sources used

in laboratory calibration studies. It is well known that there is a substantial energy dependence for both of these biodosimetry assays.

The background problems associated with these biodosimeters have not yet been adequately evaluated. For example, the labor intensive nature of chromosome analyses have hitherto prevented an adequate measurement of the spontaneous frequency of translocations as a function of age. Also, for the same reason, the interindividual variability is not known very well for any age. Unless reduced, these uncertainties will likely limit the use of cytogenetic biodosimetry to doses above 0.3 Sv, perhaps substantially above for older individuals. There are also background problems with EPR, including ultraviolet light exposure to teeth via sunlight (especially front teeth), and differences in signals based on sample preparation techniques. Needed work:

- Both EPR and FISH require additional characterization and calibration for confident application to RERF dosimetry, e.g., background, non-uniform dose, high-energy gammas, etc..

- RERF should collect and archive samples of teeth and blood. A coordinated effort should be undertaken to anticipate future RERF dosimetry needs.

- At this time, RERF should continue EPR and FISH measurements on samples from selected survivors. The main purpose should be to provide additional individual-specific intercomparison data for the two methods.

- Following additional characterization and calibration, RERF should consider the use of EPR and FISH biodosimetry to supplement the physical dosimetry.

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